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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,253	MILNER, ANNE JOSEPHINE	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *4-6 and 24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 7-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I, siRNA and p53, in the reply filed on 9/23/09 is acknowledged.

Claims 4-6 and 24-26, as well as the subject matter of the pending claims that is not directed to the elected invention, is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/23/09.

Claim Rejections - 35 USC § 112 and 35 USC § 101

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11-15 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-15 and 23 provides for the use of a SIRT1 inhibitor, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it

merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 11-15 and 23 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

It is noted that should applicant amend the claims to recite steps that differ from the treatment method of claim 1, the claims will be withdrawn as being directed to a non-elected invention, as the treatment method is currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-10, and 16-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 20 is subject to the instant rejection based upon no length requirement in the instant claims for the siRNA molecule.

At the outset, it is noted that the claims do not recite a specific SIRT1 nucleotide sequence by SEQ ID NO, but rather refer to the broad genus of SIRT1 sequences.

The claims encompass a method of introducing any type of SIRT1 inhibitor to inhibit the expression of any SIRT1 sequence, as well as encompass any SIRT1 homolog or allele from any species known or yet to be discovered of SIRT1, as well as DNA genomic fragments, spliced variants or fragment that retains SIRT1-like activity.

Although the specification discloses some inhibitory molecules such as siRNA agents, antisense agents, ribozyme agents and antibody agents, the specification does not describe an adequate species of inhibitory molecules to demonstrate that applicant was in possession of the claimed molecules within the instant method at the time the invention was made. The instant genus of inhibitory molecules is very large, including aptamers, triplexes, peptides, and miRNAs, for example.

Furthermore, although the specification discloses inhibitory agents that are specific for a SIRT1 sequence, the specification does not describe such agents directed to any other species of SIRT1 to describe the instantly claimed genus of any SIRT1. Each of the instantly disclosed agents is targeted to a single sequence, although the claims are drawn to any SIRT1. One of ordinary skill in the art could not make such agents to any SIRT1 without knowledge of the sequence and knowledge of the types of inhibitory molecules. Given the breadth of sequences embraced in the instantly claimed genus, one could not envision the member agents that target such a broad genus.

Not only is applicant claiming inhibiting any SIRT1 with any type of inhibitor, but is also claiming to treat any cellular proliferative disease or any cancer with the instant method. Applicant has not described a sufficient species of proliferative diseases that have in fact been associated with SIRT1 expression alone to represent the instant genus of treating any proliferative disorder with any inhibitor of any SIRT1.

Therefore, the scope of the claimed invention is broad and the skilled artisan would not be able to envisage the entire genus claimed of agents that inhibit the expression of any SIRT1 such that the skilled artisan would recognize that the applicant was in possession of the claimed genus at the time of filing.

Claims 1-3, 7-10, and 16-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SIRT1 inhibition via SIRT1 specific siRNA transfection *in vitro*, does not reasonably provide enablement for the treatment of any proliferative disease via introducing any SIRT1 inhibitor via any mode of administration *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The instant claims are directed to introducing any SIRT1 inhibitor via any means and treating any proliferative disorder.

The claims embrace introduction of any SIRT1 inhibitor via any mode of administration with a result of treating any proliferative disorder, wherein applicant has not demonstrated that SIRT1 inhibition alone will treat any proliferative disorder or much less any cancer, as proliferative disorders and cancer are multi-factorial and would likely not be treated by SIRT1 inhibition alone.

Furthermore, with respect to the claims that are limited to siRNA molecules, the siRNA molecule has no specific length requirement or level of complementarity with any specific target, and thus embraces a huge genus of siRNA molecules that are not even targeted directly to any specific SIRT1 sequence, but rather may have a secondary effect of inhibiting SIRT1, which is a largely unpredictable effect. Even those that do have sequence specificity to a SIRT1 sequence can have much longer sequences that are complementary to a different target and thus would not likely inhibit SIRT1 expression predictably, as the claims read on long dsRNA molecules that may comprise a short segment that is targeted to a SIRT1 sequence.

The *in vivo* teachings of the specification are strictly prophetic. The specification teaches inhibition of a SIRT1 sequence expression *in vitro* via introducing a siRNA duplex targeting the sequence and resultant SIRT1 inhibition.

There is no guidance in the specification as filed that teaches how to deliver a siRNA and mediate RNA interference *in vivo*. Although applicant has demonstrated RNA interference *in vitro*, applicant is not enabled for mediating RNA interference *in vivo* by the broadly recited methods, as delivery is known in the art to be unpredictable with regards to dsRNA duplexes.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using dsRNA. Scherer et al. (Nat. Biotechnol., 2003, 21(12), pages 1457-1465) teach that antisense oligonucleotides (ODNs), ribozymes, DNAzymes and RNA interference (RNAi) each face remarkably similar problems for effective application: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the target RNAs. Scherer et al. teach that these challenges have been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can become widely accepted as a therapeutic agent.

Mahato et al. (Expert Opinion on Drug Delivery, January 2005, Vol. 2, No. 1, pages 3-28) teach that antisense oligodeoxynucleotides and double-stranded small interfering RNAs have great potential for the treatment of many severe and debilitating diseases. Mahato et al. teach that efforts have made significant progress in turning these nucleic acid drugs into therapeutics, and there is already one FDA-approved

antisense drug in the clinic. Mahato et al. teach that despite the success of one product and several other ongoing clinical trials, challenges still exist in their stability, cellular uptake, disposition, site-specific delivery and therapeutic efficacy. Mahato et al. teach that in order for siRNAs to be used as therapeutic molecules several problems have to be overcome, including: the selection of the best sequence-specific siRNA for the gene to be targeted and the ability to minimize degradation in the body fluids and tissues.

Zhang et al. (Current Pharmaceutical Biotechnology 2004, vol. 5, p.1-7) reviews the state of the art with regard to RNAi and has this to say about use in mammalian cells. "Use of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

As outlined above, it is well known that there is a high level of unpredictability in the RNAi art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a broad method of mediating RNA interference encompassing *in vivo* treatment effects.

MPEP 2164.01
Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Also, MPEP 2164.01(a)
A conclusion of lack of enablement means that, based on the evidence regarding each of

the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of RNA *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful RNA interference or treatment of such a broad scope of diseases. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the **full scope** of the claimed invention without undue experimentation (see MPEP 2164.01(a)).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7-10, 16-19, 21, and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Guarente et al. (US 2005/0136429 A1).

The instant claims are directed to a method of treating a proliferative disease, more specifically cancer, more specifically colorectal carcinoma, via administering a SIRT1 inhibitor to an individual in need thereof. The claims are further directed to SIRT1 inhibitors, more specifically siRNA molecules.

Guarente et al. teach inhibitors of SIRT1 and specifically teach that exemplary agents include siRNA molecules that have a sequence of at least 19 nucleotides that is complementary to a sequence encoding SIRT1 (as well as polypeptides, antibodies, nicotinamide or vitamin b3), each of which are SIRT1 inhibitors (see paragraph [0043], for example).

It is noted that claims 8 and 9 are anticipated by a teaching of any SIRT1 inhibitor, as the remainder of the claims recite intended use, which does not materially alter a compound of a compound claim.

Guarente et al. teach cells containing the siRNA molecules that are specific to human SIRT1 in an amount effective to alter SIRT1 activity in the cell (see paragraph [0078] and example 5, for example) and teach compositions comprising the siRNA molecule and a pharmaceutically acceptable excipient or diluent.

Guarente et al. teach a human SIRT1 mRNA target sequence and teach that siRNA molecules targeting the SIRT1 mRNA sequence are used to treat diseases associated with SIRT1 expression.

Guarente et al. teach that such diseases include colorectal cancer (see paragraph [0112], for example).

Guarente et al. teach that siRNA molecules, antisense molecules, and ribozymes, can decrease the expression of SIRT1 in a cell or subject, wherein the subject can be treated with the compound that modulates the expression of the target nucleic acid (see paragraphs [0254]-[0260], for example).

Therefore, the instant claims are anticipated by Guarente et al.

Art of Interest

Tamai et al. (US 2003/0082668 A1) teach that SIRT1 inhibitors in general are potentially effective anti-cancer agents via enhancing p53 function (see Example 4). Tamai et al. is not applied as prior art because Tamai et al. does not teach any specific SIRT1 inhibitor. However, Tamai et al. is evidence that it was known to inhibit SIRT1 to enhance p53 function.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571) 272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Primary Examiner
Art Unit 1635

/AMY BOWMAN/
Primary Examiner, Art Unit 1635